STUDY SYNOPSIS

PRIMARY INVESTIGATOR	Pr R Coriat, MD, PhD, Gastroenterology and digestive oncology unit, université Paris Descartes, CHU Cochin, Paris, France. GTE : Groupe des Tumeurs Endocrines
TITLE	**Epidemiological study of the therapeutic management of well-differentiated grade 3 (WHO classification) neuroendocrine digestive tumors from the prospective data of the French neuroendocrine tumors registry (GTE).**
JUSTIFICATION / CONTEXT	Digestive neuroendocrine tumors are rare tumors and defined by the expression of specific diagnostic biomarkers (Baudin et al. 2007, Modlin et al., 2008, Yao et al., 2008). Cell differentiation is a major prognostic marker of neuroendocrine tumors (Madeira et al., 1998, Travis et al., 1998, Rindi et al., 1999, Lepage et. Al, 2004, Faggiano et al. 2007). Indeed, regardless of the stage and the location of the primary tumor, it has been highlighted that a well-differentiated lesion had a better prognosis than a poorly differentiated lesion (Madeira et al., 1998, Mitry et al. 1999 Rindi et al., 1999, Lepage et al., 2004, Faggiano et al., 2007, Yao et al., 2008). In 2010, the WHO classification of neuroendocrine tumors was reviewed and validated the crucial role of two other prognostic markers: the proliferation index and the Ki-67 index (Travis et al, 1998, Ekeblad et al. 2008, Strosberg et al., 2009, Panzuto et al., 2011, Raymond et al., 2011, Yao et al., 2011). The 2010 WHO Classification defined three groups of tumor according to the combination of the morphological characteristics and the mitotic index and/or the Ki-67 index (Rindi et al., 2010): Grade 1 and 2 corresponded to well differentiated neuroendocrine tumors whereas grade 3 corresponded to poorly differentiated lesions entitled neuroendocrine carcinomas (NEC). It was assumed that no well-differentiated neuroendocrine tumor with a mitotic- or a Ki-67- index above 20% existed. Thus, the 2010 WHO classification classified most cases of digestive neuroendocrine tumors. Recently, a proportion of neuroendocrine tumors corresponding to grade 3 neuroendocrine tumors with a proliferation- or Ki-67 index > 20% and with a well-differentiated morphology have been identified (Vêlayoudom-Cephisus et al., 2013). This entity has been partially explored and may have a different survival than grade 3 NEC (41 months versus 17 months, p = 0.34) (Vêlayoudom-Cephisus et al, 2013.). Furthermore, targeted therapies, everolimus (Raymond et al., 2011), sunitinib (Yao et al., 2011) and bevacizumab (Ducreux et al., 2014, Mitry et al., 2014) used in pancreatic neuroendocrine tumors have not been assessed in this case. The TENpath network is a pathological network whose goal is the systematic reading of all diagnosed cases of neuroendocrine tumors. As part of this network, nearly 3.000 neuroendocrine tumors were reviewed by pathologist experts (Scoazec et al Présentation ENETS, 2014). Of all the reviewed tumors, 167 were identified as well-differentiated grade 3 neuroendocrine tumors, observed Ki-67(5.6%) confirming the existence of this entity. The TENpath network included patients well-differentiated grade 3 neuroendocrine tumors who received either a curative surgery or a chemotherapy. Therefore two sub-groups will be distinguished: (i) patients who received a curative surgery and (ii) patients with metastasis who received chemotherapy. Treatment and follow-up of well-differentiated grade 3 tumors are not consensus-based and recommendations are exclusively based on experts'opinions. The purpose of this study is to defined the characterization of this entity and evaluate the efficacy of chemotherapy on well-differentiated grade 3 digestive neuroendocrine tumors identified from the TENpath network.

	We recently highlight in a position paper the lack of data in well-differentiated grade 3 digestive neuroendocrine tumors, justifying the interest of the present study (Coriat et al., The oncologist, 2016). Results will help physicians in the choice of the optimal treatment. Platinum based chemotherapy will be evaluated. Platinum based chemotherapy is the treatment of choice of poorly differentiated neuroendocrine tumor (Moertel 1991, Mitry 1999). Meantime, Cassier et al confirmed the usefulness of platinum based chemotherapy in well-differentiated neuro endocrine tumor (Cassier et al, 2009). The effectiveness of platinum therapy will be evaluated. The median overall survival of patients with grade 1 or 2 well differentiated GEP NET is more than 23 months whereas it is 16 in poorly differentiated tumor (Cassier et al, 2009; Basturk et al, 1991). The present study will identified the survival of this entity.
OBJECTIVES	**The primary objective** is : To compare the median of overall survival of Well-differentiated grade 3 GEP NET patients who receive first line platinum based chemotherapy versus patients receiving first line non-platinum chemotherapy. **The secondary objective** are : - To compare the objective response rate of patients receiving first line platinum based chemotherapy versus patients receiving first line non-platinum chemotherapy. - To compare the median progression free survival of patients receiving first line platinum based chemotherapy versus patients receiving first line non-platinum chemotherapy - To describe and compare hormonal symptoms of patients receiving first line platinum based chemotherapy versus patients receiving first line non-platinum chemotherapy - To identify biological or pathological markers of a poorest prognosis of platinum based chemotherapy versus patients receiving first line non-platinum chemotherapy - To describe treatment procedures for patients with well-differentiated grade 3 neuroendocrine digestive tumors receiving first line platinum based chemotherapy versus patients receiving first line non-platinum chemotherapy, including second line chemotherapy, chemoembolization and others
STUDY DESIGN	This is a retrospective study from cases recorded in the national endocrine tumors registry (GTE) and the TENpath registry, and where patients are prospectively included in the cohort since 2011.
INCLUSION CRITERIA	Well-differentiated grade 3 neuroendocrine digestive tumors recorded in the national registry of endocrine tumors (GTE) and the TENpath registry receiving first line chemotherapy
NON INCLUSION CRITERIA	o Digestive neuroendocrine tumors Grade 1-2 o Poorly differentiated digestive neuroendocrine tumors o Patient who underwent a curative surgery o Other non-digestive neuroendocrine tumors
STUDY PROCEDURES	▪ Record of individual data from every case recorded in the national registry. ▪ Monitoring of the data by the data managers in the 15 regional subdivision of the registry. ▪ Centralisation and monitoring of the data by a national data manager. ▪ Statistical analysis by the clinic investigational center of the Cochin teaching hospital in the University Paris Descartes, Paris, France
STUDY ENDPOINTS	**The primary endpoint** is a comparison of the median Overall Survival (OS) in patients receiving first line platinum based chemotherapy compared to patients receiving first line non-platinum chemotherapy. Overall survival in patients receiving first line chemotherapy is defined by to the time from first-line palliative chemotherapy to death. **The secondary endpoint are:** ➢ Comparison of the objective response rate (ORR) at 3 months and 6 months in patients receiving first line platinum based chemotherapy compared to patients receiving first line

	non-platinum chemotherapy. The objective response rate is defined as the proportion of patients who achieved a complete response (disappearance of all target tumors) or partial response (≥ 30% decrease in the sum of the longest diameters of target tumors) or stable disease based on RECIST 1.1 criteria ➢ Comparison of the median progression free survival in patients who received first line platinum based chemotherapy versus those who receive a non-platinum based chemotherapy ➢ Comparison, at baseline, of hormonal symptoms among patients who received first line platinum based chemotherapy and those who receive a non-platinum based chemotherapy. The evaluation would be a comparison performed symptoms by symptoms. ➢ Identification at baseline of biological, pathological or clinical markers of a poorest prognosis. This analyse will be controlled by the type of chemotherapy received. ➢ Description of : o the localization of the tumor, functional or non-functional neuro-endocrine tumors status, the Ki67 level, the mitotic index, the number of metastases, the number and the location of metastasis sites, radiologic and functional imaging (octreoscan, PET scan, DOPA-PET and others), the serotonin and chromogranin A level at baseline o The treatment procedures will include the number of different chemotherapy lines received, the prescription of chemotherapy alone or not (chemotherapy followed by chemoembolization is allowed) ➢ An analysis per tumor site would be performed
NUMBER OF SUBJECTS	About 200 Total patients number : 248 Patients' number in groupe 1 : 124 Patients' number in groupe 2 : 124
NUMBER OF CENTRES	15
STUDY DURATION	➢ Study start: January 2017 ➢ Collection of data: 1.5 years ➢ Statistical analysis, redaction and submission of paper and abstract for meetings (JFHOD, GTE, ENETS, ASCO): 12 months
STATISTICAL ANALYSIS	▪ Univariate analysis of factors affecting the treatment choice (the localization of the tumor, the Ki67 level, the mitotic index, the number of metastases, the number of metastasis site, the serotonin and chromogranin A level at baseline) ▪ Multivariate analysis with a Cox model ▪ Survival and survival without progression using Kaplan Meier method ▪ Comparison of survival curves (OS + PFS) with Log Rank test
EXPECTED BENEFITS	▪ Article in peer review journal ▪ Better knowledge and understanding of these rare tumors ▪ Relevance of the different treatments and evolution in time. The choice of the first line of chemotherapy: type, reason, effect and relevance. Proportion of patients who undergo a second line. The choice of the second line. The overall benefit of the chemotherapy in well differentiated Grade 3 neuroendocrine tumors will be interpreted in light of grade 1-2 well differentiated and poorly differentiated neuroendocrine tumors. ▪ Discussion for adapted guidelines

References:

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